Remarks/Arguments

1. Response to the restriction requirement: The Applicants recognize the Examiner's position that the claims as restricted have now been made final. The Applicants respectfully maintain their election of claims identified in Group 1 [claims 1 (in part), 2-11 and 27-31] with traverse for the reasons set forth in their response of July 11, 2006. However, the elected claims have been amended to better identify the claimed subject matter. Applicants reserve their rights to file a divisional application directed to all non-elected claims.

2. Claims 1-11 have been rejected as being anticipated by Takaya, et al. The Examiner contends that Takaya, et al., disclose "...a method of treating protozoan infection by administering an effective amounts of quinazolinone compounds such as febrifugine, Df-1(3)." *See* Examiner's Office Action of October 16, 2006.

The Examiner's rejection is respectfully traversed. The Applicants have amended claims 1-6 and 27-31, and cancelled claims 7-11, to better identify the subject matter of the claimed invention. Support for the amendments can be found on pages 10 through 17 of the Applicants' specification. The febrifugine/halofebrifugine/isofebrifugine derivatives listed in the specification, on pages 11-15, are not similar to the derivatives cited by Takaya, et al., and, thus, Takaya, et al., cannot anticipate these derivatives. Takaya, et al's, teaching of Df-3's potency is based on its stereochemistry and rate of metabolism: "It is found that their structures differ only in the stereochemistry at the 3' and 10' positions...it was assumed that a different rate of metabolism of the samples administered intraperitoneally is responsible for the difference in their activities in vivo." *See* Takaya, et al., at 3164. Based on Takaya's disclosure, one of ordinary skill would not be motivated to anticipate or find the present inventors' isolates obvious, as they

are markedly different in structure from those taught by Takaya, et al. This position is also bolstered by the fact, known to one of ordinary skill, that not all derivatives of febrifugine show efficacy against *P. falciparum* or *P. berghei*. The present inventors have found that their analogs show "interference to the parasite's cellular signal transduction systems." *See* Specification at 10. Additionally, these analogs also show lower toxicity to mammalian neuronal and macrophage cells, as is recited in currently amended claim 1. *See* Specification at 17. Takaya, et al., do not disclose such activity because they only disclose initial potency. "These results support the view that it is a promising new lead compound..." (emphasis added), indicating necessary further investigations. *See* Takaya, et al., at 3165. Thus, Takaya, et al., do not anticipate the Applicants' claims, and the Examiner's rejection is overcome.

3. Claims 1-2 and 7 have been rejected as being anticipated by Takeuchi, et al. The Examiner contends that Takeuchi, et al., disclose a method of treating protozoan infections that are supported by *in vitro* and in *vivo data*.

The Examiner's rejection is respectfully traversed. Please note that claims 1 and 2 have been amended to recite derivatives/analogs of febrifugine and isofebrifugine as per the Applicants' specification. Additionally, please note that claims 7-11 have been cancelled. Takeuchi, et al., is a teaching reference showing the history and synthesis of febrifugine as well as its "well-known" candidacy as antimalarials. *See* Takeuchi, et al., at 65. Takeuchi, et al., do not disclose that all derivatives known or unknown will be effective against *P. falciparum* or *P. berghei*. Nor do Takeuchi, et al., teach the specific derivatives or their efficacy or treatment as disclosed by the present inventors. Thus, Takeuchi, et al., cannot anticipate the present invention, and the Examiner's rejection is now overcome.

4. Claims 1-2 and 7 have been rejected as being anticipated by Kobayashi, et al. The Examiner contends that Kobayashi, et al., disclose methods for administering febrifugine or isofebrifugine as antimalarials, particularly, *P. falciparum*.

The Examiner's rejection is respectfully traversed. Claims 1 and 2 have been amended to better recite the subject matter of the invention. Claim 7 has been cancelled. Kobayashi, et al., disclose derivatives of febrifugine. However, those derivatives are markedly different from those of the present invention, as shown on pages 11-15 of the Applicants' specification, and do not disclose lower mammalian toxicity as per the present invention. Thus, Kobayashi, et al., do not anticipate the present invention, and the Examiner's rejection is overcome.

5. Claims 27-31 have been rejected as being obvious over Takaya, et al., in view of Takeuchi, et al. The Examiner contends that it would have been obvious for one of ordinary skill to have administered a quinazolinone compound as recited in claim 27 because "febrifugine is known to be useful in the treatment of protozoan infections, wherein protozoa is *plasmodium falciparum* or *plasmodium berghei*... Thus one of ordinary skill... would reasonably expect that the derivatives of febrifugine would have similar properties and therapeutic effects as febrifugine... therefore...the instant particular quinazolinone derivative would have same or substantially similar beneficial therapeutic effects and usefulness as febrifugine in methods for treating protozoan.....based on the reasonable expectation that structurally similar species usually have similar properties...in fact similar properties may normally be presumed when compounds are very close in structure." *See* Examiner's October 16, 2006, Office Action at 6.

The Examiner's rejection is respectfully and strongly traversed. Both Takaya, et al, and Takeuchi, et al., do not support the Examiner's position. Takaya, et al., clearly and distinctly state that different febrifugine analogs have varying efficacies and where Df-3 was significantly

more potent than Df-4, febrifugine and isofebrifugine against *P. falicparum*. *See* Takaya, et al., at 3163. Thus, Takaya, et al., acknowledge that, even if derivatives of febrifugine have similar structures, they do not have similar efficacies. Takeuchi, et al., provide a historical synopsis of febrifugine, including its known antimalarial activity, concluding that febrifugine is more potent than its derivatives. *See* Takeuchi, et al., at 73. Thus, Takeuchi, et al., directly contradict Takaya, et al. This contradiction shows that (a) the efficacies of similar and dissimilar febrifugine derivatives are not predictable and therefore unobvious to one of ordinary skill in the art; (b) the teachings of Takaya, et al., cannot be combined with that of Takeuchi, et al.; and (c) the analogs of the present invention could not be presumed to have known efficacies, as they are unobvious dissimilar structures to those taught by Takaya, et al., and Takeuchi, et al. Based on the combined teachings of Takaya, et al., and Takeuchi, et al., one of ordinary skill would not have a reasonable expectation that the present invention would possess similar properties as that disclosed in the prior art.

For the reasons given above, the Examiner's rejections have been overcome. Early allowance of the claims is respectfully requested. Please direct any written communication to Ms. Elizabeth Arwine, Esq.; Staff Judge Advocate Office; Department of the Army; U.S. Army Medical Research and Materiel Command; 504 Scott Street; Fort Detrick, Maryland 21702-5012. Please direct all telephonic communications to Ms. Abby Bhattacharyya, Esq., at (410) 964-9553.

Sincerely,

04-12-07
Date

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